Dimeric Natural Products

DOI: 10.1002/anie.201402384

Double Trouble—The Art of Synthesis of Chiral Dimeric Natural Products**

Tim Wezeman, Kye-Simeon Masters, and Stefan Bräse**

Diels–Alder reactions · dimerization · natural products · oxidative coupling · secalonic acid

Dedicated to Professor Armin de Meijere on the occasion of his 75th birthday

The last century brought us a fascinating and broad spectrum of highly complex natural products. A particularly challenging and appealing class comprises dimeric natural products consisting of two complex monomeric units. Many such compounds have been identified as having novel biological properties.[1] Several syntheses of such chiral dimeric natural products consisting of achiral subunits have been reported in the last decade (**1**–**4**, Figure 1).[1b–d] In addition, the biosynthetic origins of several of the members of this class—mostly oxidative dimerization processes—have been elucidated in detail.[2]

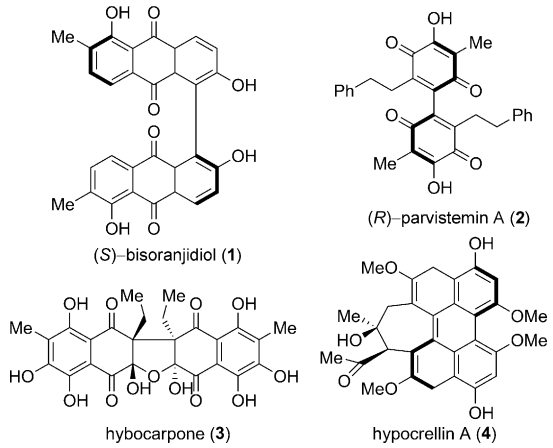
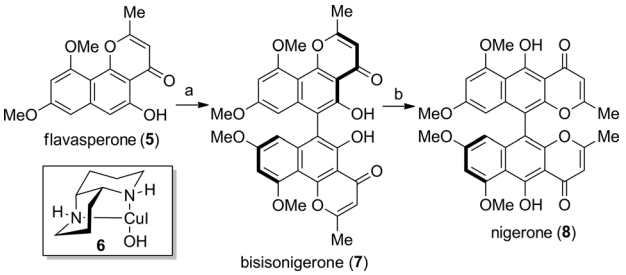


Figure 1. Examples of chiral dimeric natural products consisting of achiral monomers.

It has been shown that biomimetic oxidative coupling processes are not always suitable for chemical total synthesis using monomeric building blocks, as there are frequently problems with regioselectivity and unwanted side reactions (C–O formation etc.). However, such oxidative coupling pathways have proven highly effective for the synthesis of selected dimeric natural products, for example in the enantioselective synthesis of bioactive mold isolates bisisonigerone and nigerone (**7** and **8**, Scheme 1) described by Kozlowski, Bringmann, and co-workers.[3] In their synthesis, flavasperone monomer **5** was heated with the chiral 1,5-diaza-*cis*-decalin copper catalyst **6**. In the final step, base-catalyzed isomerization of bisisonigerone (**7**) to the more stable nigerone (**8**) was conducted in methanol with sodium hydroxide at 70 °C. Circular dichroism (CD) spectral analysis of **8** confirmed its absolute stereochemistry as (*M*)-(−).

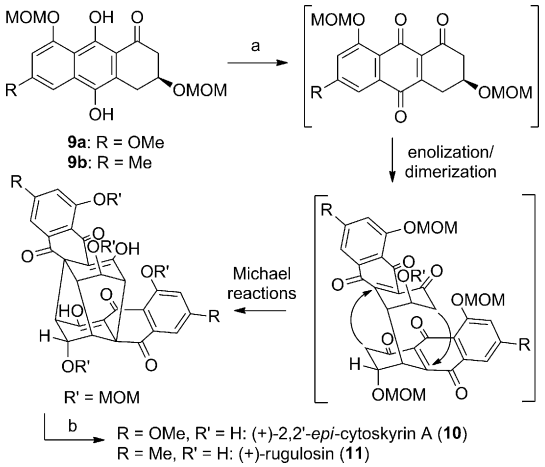


Scheme 1. Kozlowski and Bringmann's synthesis of bisisonigerone and nigerone. a) Copper complex (*S*,*S*)-**6** (1.1 equiv), CH_2Cl_2, air, 50 °C, 6 days, 60%, 80% *ee*; b) NaOH (aq.), methanol, 70 °C, 16 h, 50%, 90% *ee*.

Another example of dimeric natural product synthesis relying on the oxidative coupling of monomeric subunits is Nicolaou's cytoskyrin cascade (Scheme 2) using manganese(IV) oxide and triethylamine.[4] The fungal metabolite cytoskyrin is a congener of a large class of dimeric natural products which formally can be derived from anthraquinones. The cytoskyrin cascade, most likely consisting of an enolization, dimerization, and oxidation followed by two intramolecular Michael reactions, was applied to monomer **9a** and **9b** to synthesize (+)-2,2′-*epi*-cytoskyrin A (**10**) and (+)-ru-

[*] T. Wezeman, Prof. Dr. S. Bräse
Institute of Organic Chemistry (IOC)
Karlsruhe Institute of Technology (KIT)
Fritz-Haber-Weg 6, 76131 Karlsruhe (Germany)
E-mail: braese@kit.edu
Dr. K.-S. Masters
Chemistry, Physics and Mechanical Engineering
Faculty of Science and Engineering
Queensland University of Technology (QUT)
GPO Box 2434, Brisbane, Queensland, 4001 (Australia)
E-mail: kye.masters@qut.edu.au
Prof. Dr. S. Bräse
Institute of Toxicology and Genetics (ITG)
Karlsruhe Institute of Technology (KIT)
Eggenstein-Leopoldshafen (Germany)

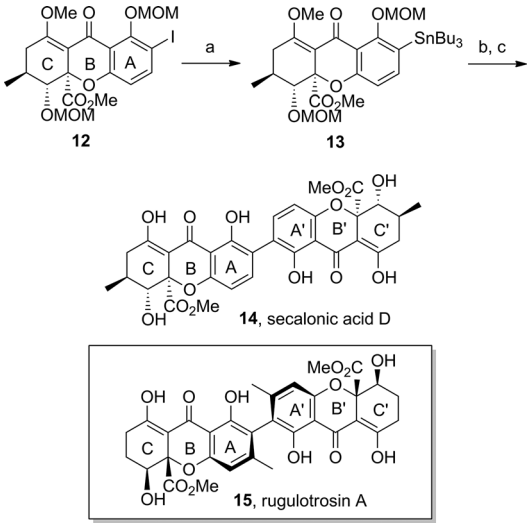
[**] We acknowledge continuous funding through the DFG (BR 1750) and the Helmholtz Association. K.-S.M. acknowledges a Vice Chancellor's Research Fellowship from QUT and T.W. acknowledges the Marie-Curie ITN ECHONET (grant no. 316379).



Scheme 2. Nicolaou's synthesis of the cytoskyrin core applied to the synthesis of (+)-2,2′-*epi*-cytoskyrin A and (+)-rugulosin. a) MnO_2 (1.5 wt equiv), CH_2Cl_2, 25 °C, 10 min; then MnO_2 (1.5 wt equiv), Et_3N (5.0 equiv), 25 →48 °C, 12 h, 60–50%; b) HCl (conc.), MeOH, THF, 60 °C, 12 h, 93–98%. MOM = methoxymethyl.

gulosin (**11**) in 60% and 50% yield, respectively. In both cases a side reaction producing an aromatized version of **9** was also found. (+)-Rugulosin is known to exhibit both anti-HIV and cytotoxic properties and even though (+)-2,2′-*epi*-cytoskyrin A is not a natural product, Nicolaou et al. comment that it would not be surprising if it is someday indeed found in nature.

The recently reported synthesis of secalonic acids D and A (**14**, Scheme 3, and *ent*-**14**, not shown) by Porco and coworkers[5] represents a milestone in the synthesis of dimeric natural products as the monomeric units are chiral. This synthesis comprises the first total synthesis of a naturally occurring ergochrome xanthone dimer, a class of compounds



Scheme 3. Porco's synthesis of secalonic acids D (**14**) and D (*ent*-**14**). a) $[Pd_2(dba)_3]$ (10 mol%), $PtBu_3$ (40 mol%), nBu_4NI (50 mol%), $(SnBu_3)_2$ (2.0 equiv), 1,4-dioxane, 50 °C, 4 h, 51%; b) CuCl (5.0 equiv), DMA, air, RT, 12 h, 60%; c) 3 M HCl/acetone, 60 °C, 20 h, 81% (for *ent*-**14**: 3 M HCl/MeCN, 60 °C, 30 min, 85%). dba = Dibenzylideneacetone, DMA = dimethylacetamide.

that has been studied for over a century since its discovery in extracts of *Claviceps purpurea* by Kraft[6] and has fascinated synthetic chemists for the past forty years following the synthesis of the first hemisecalonic derivative.[8a] The secalonic acids and other ergochromes have been the subject of hundreds of published studies focusing on both their fascinating structural features and biological activities, including interactions with a plethora of diverse medical conditions and pronounced mutagenic and teratogenic properties.[7]

The Porco synthesis built upon the successful synthesis of the monomeric unit blennolides, previously reported by themselves[8e] and others,[8] and involved first the construction of a hemisecalonic derivative, then conversion to iodide **12** and stannane **13**. The synthesis featured a copper-catalyzed C–C bond-forming reaction between two equivalents of stannane **13** under oxidative conditions as the key dimerization step. This method solved a significant synthetic challenge, as the unique electronic nature of the monomeric xanthone framework had previously been shown to not be suitable for more direct oxidation reactions.[9] Since the precursor **12** can be pre-activated at the *ortho*-position (with trialkyl stannane), the dimerization is thus reliably regioselective. The identity with the natural product was proven by comparison with authentic samples.

This elegant synthesis of secalonic acid opens an avenue to a number of other natural products with similar stereochemistry. However, it should be noted at this point that nature also supplied us with a number of related dimeric natural products not having C_2 symmetry: The secalonic acids C, F, and G, and some of the other ergochromes and ergoflavins are not available by this route as they consist of two nonequivalent monomers. The next milestone in the synthesis of chiral dimeric natural products may see the generation of compounds comprising chiral monomers, and also possessintg axial chirality, for example rugulotrosin A (**15**).[10]

Although the art of synthesis of chiral dimeric natural products still presents a great challenge to the chemical research community, ongoing advances like those represented by the achievements above provide insight and motivation for future work in this field.

Received: February 13, 2014
Published online: April 3, 2014

[1] a) Review: M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193–3207; examples: b) (*S*)-Bisoranjidiol: E. E. Podlesny, M. C. Kozlowski, *Org. Lett.* **2012**, *14*, 1408–1411; E. E. Podlesny, M. C. Kozlowski, *J. Org. Chem.* **2013**, *78*, 466–476; c) Parvistemin A: M. J. Smith, C. C. Nawrat, C. J. Moody, *Org. Lett.* **2011**, *13*, 3396–3398; d) Hypocrellin A: E. M. O'Brien, B. J. Morgan, M. C. Kozlowski, *Angew. Chem.* **2008**, *120*, 6983–6986; *Angew. Chem. Int. Ed.* **2008**, *47*, 6877–6880; e) Hybocarpone: K. C. Nicolaou, D. Gray, *Angew. Chem.* **2001**, *113*, 783–785; *Angew. Chem. Int. Ed.* **2001**, *40*, 761–763.

[2] a) W. Hüttel, M. Müller, *ChemBioChem* **2007**, *8*, 521–529; b) D. Drochner, W. Hüttel, S. E. Bode, M. Müller, U. Karl, M. Nieger, W. Steglich, *Eur. J. Org. Chem.* **2007**, 1749–1758; c) B. Franck, R. Chahin, H. G. Eckert, R. Langenberg, V. Radtke, *Angew. Chem.* **1975**, *87*, 846–846; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 819–820; d) D. Drochner, W. Hüttel, M. Nieger, M. Müller,

Angew. Chem. **2003**, *115*, 961 – 963; *Angew. Chem. Int. Ed.* **2003**, *42*, 931 – 933.
[3] a) M. C. Kozlowski, E. C. Dugan, E. S. DiVirgilio, K. Maksimenka, G. Bringmann, *Adv. Synth. Catal.* **2007**, *349*, 583 – 589; b) E. S. DiVirgilio, E. C. Dugan, C. A. Mulrooney, M. C. Kozlowski, *Org. Lett.* **2007**, *9*, 385 – 388.
[4] a) K. C. Nicolaou, C. D. Papageorgiou, J. L. Piper, R. K. Chadha, *Angew. Chem.* **2005**, *117*, 5996 – 6001; *Angew. Chem. Int. Ed.* **2005**, *44*, 5846 – 5851; b) see also E. Gravel, E. Poupon, *Eur. J. Org. Chem.* **2008**, 27 – 42; c) K. C. Nicolaou, Y. H. Lim, C. D. Papageorgiou, J. L. Piper, *Angew. Chem.* **2005**, *117*, 8131 – 8135; *Angew. Chem. Int. Ed.* **2005**, *44*, 7917 – 7921; ; d) K. C. Nicolaou, Y. H. Lim, J. L. Piper, C. D. Papageorgiou, *J. Am. Chem. Soc.* **2007**, *129*, 4001 – 4013.
[5] T. Qin, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2014**, *53*, 3107 – 3110; *Angew. Chem.* **2014**, *126*, 3171 – 3174.
[6] F. Kraft, *Arch. Pharm.* **1906**, *244*, 336 – 359.
[7] K.-S. Masters, S. Bräse, *Chem. Rev.* **2012**, *112*, 3717 – 3776.
[8] a) B. Franck, J. Stöckigt, U. Zeidler, G. Franckowiak, *Chem. Ber.* **1973**, *106*, 1198 – 1220; b) K. C. Nicolaou, A. Li, *Angew. Chem.* **2008**, *120*, 6681 – 6684; *Angew. Chem. Int. Ed.* **2008**, *47*, 6579 – 6582; c) E. M. C. Gérard, S. Bräse, *Chem. Eur. J.* **2008**, *14*, 8086 – 8089; d) W. Zhang, K. Krohn, Z. Ullah, U. Flörke, G. Pescitelli, L. Di Bari, S. Antus, T. Kurtan, J. Rheinheimer, S. Dräger, B. Schulz, *Chem. Eur. J.* **2008**, *14*, 4913 – 4923; e) T. Qin, R. P. Johnson, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2011**, *133*, 1714 – 1717; f) L. F. Tietze, L. Ma, J. R. Reiner, S. Jackenkroll, S. Heidemann, *Chem. Eur. J.* **2013**, *19*, 8610 – 8614.
[9] H. Sahin, M. Nieger, S. Bräse, *Eur. J. Org. Chem.* **2009**, 5576 – 5586.
[10] M. Stewart, R. J. Capon, J. M. White, E. Lacey, S. Tennant, J. H. Gill, M. P. Shaddock, *J. Nat. Prod.* **2004**, *67*, 728 – 730.

